Cover Page
Study Title: Rotational Thromboelastometry for the Transfusion Management of Postpartum Hemorrhage After Vaginal or Cesarean Delivery
NCT03064152
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SUBJECT ENROLLMENT

Patients who meet eligibility criteria will be identified by the investigators. Their obstetricians will be asked whether we may approach the patients prior to hospital admission. With this permission, eligible patients may be approached in person or by phone by a research assistant (non-physician) or a co-investigator (licensed physician) informed about the study, and a recruitment letter and consent form will be given to the patients for review. This will occur in person, by mail (at a patient's request), or upon arrival on labor and delivery. With these methods, subjects will be provided ample time to consider participation in the study. Patients who have been provided the recruitment letter and consent form prior to admission will then be approached when they are admitted to the hospital.

Informed consent will be obtained from all subjects prior to enrollment after a thorough explanation and discussion of the study plan with the physician investigator. Subjects will be given the opportunity to ask any questions and will be encouraged to discuss their decision to participate with any of their treating physicians. Following satisfactory completion of the above noted recruitment procedures, subjects will be consented by the principal investigator or physician co-investigator at least two hours prior to the patient's vaginal or cesarean delivery on the labor floor or in the triage/pre-operative area of the Center for Women and Newborns.

This study will only be conducted in women. Minorities will be approached with the use of available translators for non-English speaking subjects. No other vulnerable populations will be specifically targeted, nor will any one group bear a disproportionate share of the burdens or benefits of the research.

STUDY PROCEDURES

Patient's providers will first approach them to evaluate their willingness to participate in the study by providing the patient with a study information letter with an 'opt out' mechanism. Subjects will then be approached. Subjects will then be assessed for study eligibility as described above. Eligible and consenting patients who experience PPH will then be randomized to "control" or "ROTEM" groups by a computer generated randomization scheme. The obstetrician, nurse, and anesthesiologist involved in the cases will not be blinded to the study solution assignments. An investigator not involved in the case will conduct ROTEM measurements at any time standard coagulation labs are sent.

The management of PPH can occur in the OR or in the labor room. If a patient hemorrhages after vaginal delivery, we do occasionally draw a PPH lab panel [and study lab for a randomized patient] in the labor room. Many times, these patients are then transported to the operating room for further management. The ROTEM device is stationed between labor ORs 3 and 4. A patient sample in a blue vacutainer tube is taken to the ROTEM device from the labor room or the OR, by a co-investigator. At the time of hemorrhage recognition, a blue top and a purple top are drawn and sent to central lab (for any patient, in the study or not). Study patients have one additional blue top drawn for their ROTEM test. By collecting the study sample at the same time our routine samples are sent, study-specific intervention (new IV access solely for study purposes) is avoided. At maximum, we will draw less than 1 tablespoon extra blood for ROTEM® testing during the entire course of this research study. Patients will receive standard of

care for labor and delivery, cesarean delivery, and postpartum care. Patients admitted for delivery at Brigham and Women's Hospital have baseline labs drawn as standard of care. Baseline labs include: type and screen, serum hemoglobin, platelet count, fibrinogen, activated partial thromboplastin time (aPTT), prothrombin time (PT), and red top test.

Transfusion will be based on standard of care utilizing clinical criteria of hemodynamics (noninvasive blood pressure, heart rate, arterial line if deemed clinically useful) and coagulation labs (PT, aPTT, fibrinogen, complete blood count, red top test) in both groups. In addition to standard of care, additional ROTEM blood assays will be performed at any time routine coagulation labs are sent. Providers in the control group will be blinded to ROTEM results. Providers in the ROTEM group will receive real-time ROTEM results and a previously validated ROTEM-based transfusion algorithm for PPH (Mallaiah et al 2015). The investigator will quantitatively measure blood loss during the vaginal or cesarean delivery using a previously validated method (Triton System, Gauss Surgical Inc. Los Altos, CA). The total intravenous fluids given from start to conclusion of the study period will be recorded. The use of vasopressors, uterotonic agents, and antiemetic agents will be recorded.

Study Endpoints

Early Endpoints

Two definitions of early endpoints will be utilized:

1. Subject decision for withdrawal from participation at any time.
2. Any operative or medical condition changes prior to or during the entire study period deemed unacceptable by the obstetrician, anesthesiologist, or physician investigator.

Primary Endpoint

1. Number of blood products transfused, t_0 = diagnosis of PPH by criteria defined above; t_{final} = 48h after onset of PPH.

Secondary Endpoints

1. ROTEM values drawn at the time of the last blood sampling within 4 hours from leaving the operating room or within 4 hours from the last blood transfusion, whichever occurs later.
2. Intraoperative blood loss (visual estimate in suction canister and sponges, EBL, and pre- vs post-delivery hemoglobin values).

Maternal morbidity: admission to the intensive care unit postpartum, need for additional postoperative procedures for bleeding, hysterectomy, postoperative infection, transfusion reaction, acute kidney injury, hypovolemic shock, vasopressor requirement, or mortality. Patient records at the 6-week postpartum visit will be reviewed for any incidence of delayed hemorrhage after hospital discharge.

All clinical and other data obtained during this study will be considered confidential. Procedures to limit access to subject charts and information from the study will be in place. The names of study participants will be known only to the investigators. No information regarding the identity of individual subjects will be utilized for publications.

Outcomes considered serious adverse events including hemodynamic instability requiring epinephrine or norepinephrine or resulting in loss of consciousness or cardiovascular collapse, or allergic or anaphylactic reactions may all fit the criteria for withdrawal from the study. Each of these events will warrant an evaluation by the PI; please see "monitoring section" below.

Subject Costs

There will be no costs to the subjects related to the conduct of this study, as there are no additional medications or tests that are not already the routine standard of care at Brigham and Women's Hospital. ROTEM testing used in the study group will be performed by qualified obstetric anesthesiology physicians under the supervision of a certified lab director, with funding from the department of Obstetrics and Gynecology. Otherwise, subjects and/or their insurance companies will be responsible for the routine medical and surgical procedures and care associated with their cesarean delivery or vaginal delivery and hospitalization.

BIOSTATISTICAL ANALYSIS

ROTEM values between the control and ROTEM groups will be compared as quantitative outcomes against pre-established ranges for each value in pregnancy and choice of product transfused with or without the ROTEM protocol will be compared.

Sample size calculations for the primary outcome of number of blood products transfused is based on a surrogate finding of reduction in transfused products in a matched study population that was demonstrable using 50 subjects per group). We anticipate that by recruiting the same number of patients as in this previous study (100 patients total), we will reproduce the effects of reducing blood product transfusion. A group size of n = 50 will give a power of 80% (beta = 0.2) based on a 5% significance (alpha 0.05%); 100 subjects per group will be recruited with the goal of completing 50 subjects in the control group and 50 subjects in the ROTEM group.

Data will be analyzed using one-way analysis of variance and Kruskal-Wallis tests as appropriate. Analysis of variance will be used to compare intergroup demographic data, estimated blood loss (EBL), ROTEM values, and hemoglobin values. All statistical analyses will be performed using Statview v 5.0 for Macintosh. A P value < 0.05 will be considered significant and all data will be reported as mean ± standard deviation.

Note: the study was stopped prior to our goal enrollment of 100 patients (N = 50 per group). Our total recruitment was N = 49; 26 control, 23 ROTEM due to slower than anticipated recruitment (3 years and 1 month). The decision to stop the trial early was not out of concern for patient safety or adverse events. We are aware that trials stopped earlier than anticipated may dramatically overestimate the effect of an intervention. However, given our lack of impact on our primary outcome in the intervention group we can infer that additional recruitment would yield results of the same clinical outcome (no effect).